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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/083,476	02/27/2002	Roger N. Piasio	ISA-102.01	4777

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FOLEY HOAG, LLP
PATENT GROUP (w/ISA)
155 SEAPORT BLVD.
BOSTON, MA 02210-2600

EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/083,476	PIASIO ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 06/05/09 in response to the final Office Action mailed 03/05/09.

Status of Claim(s)

2) Claim 22 has been amended via the amendment filed 06/05/09.

Claim is 22 is pending.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Withdrawn

5) The rejection of claim 22 made in paragraphs 13(a) to 13(g) of the Office Action mailed 03/05/09 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim and/or Applicants' arguments.

Rejection(s) Maintained

6) The rejection of claim 22 made in paragraph 11 of the Office Action mailed 06/05/09 under 35 U.S.C. § 112, first paragraph, as containing inadequate written description, is maintained for the reasons set forth therein and herein below.

Applicants contend that claim 22 does not require a specificity of 90% or better 'although such a test is within the scope of claim 22'. Applicants cite *Vas-Cath, Inc. v. Mathukar*, 19 U.S.P.Q. 2d 1111 and assert that the invention for the purposes of the written description inquiry, 'whatever is now claimed'. Applicants submit that as claim 22 does not require an intended specificity of 90% or better, claim 22 complies with the written description requirement.

Applicants' argument has been carefully considered, but is not persuasive. As readily acknowledged by Applicants, a method of detecting a symptomatic *S. pneumoniae* infection in a human subject of age 12 years or less having a specificity of 90% or better is well within the scope of the instant claim. Under the provisions of 35 U.S.C. § 112, first paragraph, Applicants should have possession, at the time of the invention, of the claimed invention, i.e., a method of detecting a symptomatic *S. pneumoniae* infection in a human subject of age 12 years or less, which method has a degree of specificity and/or sensitivity that is acceptable by those of skill in the art. As set forth previously, the instant specification identifies such a method to be a detection method that maintains a high test specificity and an improved sensitivity of the test that uses urine samples from children with pneumococcal disease. See for example page lines 3-6 of page 7 of the specification, which is reproduced below [Emphasis added]:

> The objective of the modifications, which is to **maintain high specificity for diseased patient samples** and to improve sensitivity to those samples by screening out samples from healthy, but nasopharyngeally colonized, children which gave false positives in the standard NOW® test for *Streptococcus pneumoniae*.

From a review of the instant specification, it appears that at the time of the invention, Applicants did not have possession of a detection method that used one or more scrub lines positioned prior to a capture line in the sample flow path, which method yielded an art-acceptable test specificity, let alone a test specificity of 90% or better, an increased sensitivity to urine samples from children infected with pneumococci, and false positives due to nasopharyngeal pneumococcal colonization eliminated or minimized. For example, the method described in Example 3 of the instant specification is said to reduce conjugate concentration, reduce capture line concentration, and add one scrub line, whereas the method described in Example 4 is said to reduce conjugate concentration, reduce capture line concentration, and add two or three scrub lines. Table III depicts that when one scrub line was used with a scrub line antibody concentration of 0.3 to 0.6 mg/ml, 50% to 87.5% of the infected urine samples were positive, while **28% to 46% of the urine samples from nasopharyngeal carriers were also positive**, i.e., false positive. Example 3 concludes that: (a) while these tests generally showed increasing elimination of false positives with increasing concentration of the scrub line, '**the specificity of the test was *adversely affected***'; and (b) increasing the concentration of the scrub line '**did *not* remove all antigen from the false positive samples**' and it was therefore decided to try multiple scrub lines, each of

lower concentration than the 0.3 mg/ml scrub line in one series of tests in that Example. Table IV depicts the results from Example 4. Although the use of 3 scrub lines at an antibody concentration of 0.1 mg/ml at each scrub line was effective in wholly eliminating false positives, it also ***eliminated 80% of the positive*** **samples**. The results from Table IV show that the use of 2 scrub lines at an antibody concentration of 0.1 mg/ml, or above 0.1 mg/ml, i.e., 0.15, 0.2 and 0.25 mg/ml, '***adversely affected the test results on positive samples, decreasing specificity and sensitivity***'. Thus, the method of detection that used one scrub line, or 2-3 scrub lines at various antibody concentrations did not accomplish the very objective of the instant invention, i.e., maintaining an acceptable test specificity, let alone a test specificity of 90% or better, and increasing sensitivity of the test to children infected with pneumococci while eliminating or at least minimizing false positives due to nasopharyngeal pneumococcal colonization. The methods of detection that used one scrub line, or 2-3 scrub lines at various antibody concentrations did not yield a method of reasonably acceptable specificity and sensitivity, which method detected a symptomatic *S. pneumoniae* infection in a reasonably high number of human subjects of age 12 years or less, and in an acceptably low number of human subjects of age 12 years or less with nasopharyngeal pneumococcal colonization. Clearly, a detection test method that **eliminated 80% of the positive samples**, yielded positive results in as many as **28% to 46% of the urine samples from nasopharyngeal carriers,** and lacked statistically significant findings would not be accepted by those of skill in the art as a method of detecting a 'symptomatic' *S. pneumoniae* infection in human subjects of age 12 years or less, because it also detects a high percentage of asymptomatic nasopharyngeal carriers of *S. pneumoniae*. Such a detection method does not constitute an improvement to Binax NOW® bioassay, the very objective of the instant application as stated in the second full paragraph on page 7 of the original specification filed 02/27/02 and Applicants were not in possession of such an improved detection method of acceptable specificity and/or sensitivity at the time of the invention. The *prima facie* evidence for the fact that a serological detection method of such a low specificity and/or sensitivity is not accepted by those of skill in the art as a method of detecting symptomatic *S. pneumoniae* infection in human children of age 12 years or less has been made of record previously in the instant application. Documented in the state of the art are numerous reports of similar lack of specificity and/or sensitivity and the lack of success obtained with the Binax

NOW® bioassay in serologically distinguishing children with symptomatic pneumococcal pneumonia from those who are merely colonized. For instance, see below.

(A) Dowell *et al.* (*Clin. Infect. Dis.* 32: 824-825, 2001, of record) taught that the test was significantly more likely to be positive among children who were nasopharyngeal carriers of pneumococci. See abstract; Table 1; and page 824. More than half of the patients (> 50%) who did not have pneumonia but who had pneumococci in their nasopharynx had a positive result of the urine antigen detection test. See paragraph bridging 824 and 825.

(B) Similarly, Adegbola *et al.* (*Pediatr. Infect. Dis. J.* 20: 718-719, July 2001, of record) stated the following with regard to the use of Binax NOW® test (see page 719):

> ….. The detection of urinary antigen in more than one-half of the children colonized by *S. pneumoniae* indicates that a positive result from this test **does not necessarily imply active disease in children**. Thus when used in a community with high pneumococcal carriage, a positive result from Binax NOW test must be interpreted **with caution**. The two "false positive" tests in our study may indeed have been true positives because the presence of pneumococcal antigen resulting from colonization is intermittent and pneumococcal antigen could be excreted in urine after the disappearance of *S. pneumoniae* from the nasopharynx.
>
> ……. Binax NOW test would **likely be of limited value** for detection of childhood pneumococcal pneumonia in our study population. In a recent study of the etiology of pneumonia in Beijing, China, the Binax NOW test **was no more likely to be positive among children** with radiographically confirmed pneumonia than among control children, and it was **more likely to be positive** among children who were colonized by *S. pneumoniae*. The test may also be **of limited value in the diagnosis of adult pneumonia** because of the relatively high carriage rates of *S. pneumoniae* in Gambian adults. …… There was **no correlation** between the magnitude of nasopharyngeal carriage and the intensity of the color line in positive tests. [Emphasis added].

Adegbola *et al.* expressly stated that the Binax NOW *Streptococcus pneumoniae* urinary antigen test had a positive predictive value of 96% for nasopharyngeal carriage in children and a negative predictive value of 22%. See abstract. Adegbola *et al.* concluded that the Binax NOW *Streptococcus pneumoniae* urinary antigen test 'is not useful for predicting etiology of disease in populations with a high rate of nasopharyngeal carriage of pneumococci'. See abstract.

(C) Furthermore, Navarro *et al.* (*J. Clin. Microbiol.* 42: 4853-4855, 2004, abstract, of record) performed the Binax NOW immunochromatographic test (ICT) for detecting *Streptococcus pneumoniae* antigen in urine specimens from children presenting underlying pulmonary diseases with no recent pneumococcal infection and concluded that the Binax NOW

ICT assay 'is **unlikely** to be useful for **discriminating** between children with and without pneumococcal pneumonia' [Emphasis added]. See abstract.

(D) Additionally, Nariai *et al.* (*Kansenshogaku Zasshi* 78: 18-21, January 2004, abstract, of record) evaluated *Streptococcus pneumoniae* urinary antigen test in healthy children with nasopharyngeal pneumococcal carriage and found that 58.3% of the children with pneumococcal carriage and 27.3% of non-carriers had false-positive test results. Nariai *et al.* concluded that the 'test is **not likely to be useful for diagnosing the etiology of childhood acute pneumococcal pneumonia**'. See abstract.

(E) Dominguez *et al.* (*J. Clin. Microbiol.* 41: 2161-2163, May 2003, abstract, of record) evaluated the usefulness of urinary antigen detection by the ICT assay for diagnosis of pneumococcal pneumonia in children and concluded that the test is a 'nonspecific' test for the diagnosis of pneumococcal pneumonia in children. See abstract.

(F) Magentie *et al.* (*Ann. Biol. Clin.* 61: 106-109, Jan-Feb 2003, abstract, of record) evaluated the Binax NOW *Streptococcus pneumoniae* urinary antigen test in urine samples from children and adults and concluded that the 'sensitivity and specificity' of the assay 'were lower than those announced by the manufacturer'. See abstract.

(G) Hamer *et al.* (*Clin. Infect. Dis.* 61: 1025-1028, April 2002, of record) assessed the Binax NOW *Streptococcus pneumoniae* urinary antigen test in children with nasopharyngeal pneumococcal carriage and concluded as follows (see first paragraph under 'Discussion'):

> ….. rates of positive urinary antigen test results varied significantly according to the nasal colonization status of the patient. We suspect that these positive test results are due to the detection of pneumococcal antigen that originates from pneumococci colonizing the upper airways.

Hamer *et al.* further taught the following (see last two paragraphs under 'Discussion') [Emphasis added]:

> One potential shortcoming of our study was the **failure to identify** children with recent but resolving acute respiratory infections. Because pneumococcal antigens are shed for weeks after pneumonia resolves [3], recent but resolved infections might explain the false-positive urinary antigen test results for children who did not have carriage.
>
> On the basis of our results and the results of the studies from China and The Gambia [6,8], it appears that the Binax NOW *S. pneumoniae* urinary antigen test should be used **with caution** for the detection of pneumococcal pneumonia or bacteremia in young children, especially in developing countries where nasopharyngeal colonization rates are high.

As established above, the various parts of the instant specification including the examples

demonstrate that Applicants were not possession of a method of detecting a symptomatic *S. pneumoniae* infection in a human subject of age 12 years or less that uses scrub lines, capture lines, scrub line antibodies, and capture line antibodies as claimed currently, which method is either of art-acceptable specificity and/or sensitivity, or a specificity and/or sensitivity acceptably better than that of the Binax NOW® bioassay.

Furthermore, the instant specification in the third full paragraph under Example 4 conveys Applicants' *intention to run further tests* using two or three scrub lines at lower concentrations than were incorporated in the series therein, 'to *try to eliminate* false positives without adversely affecting the sensitivity and specificity of the test' toward infected patient's samples. Applicants again intend herein to 'try' combinations of 1-3 scrub lines with the capture line concentration and the optical density maintained at the level currently used for the NOW test on the premise that scrubbing out the level of antigen in the urine sample of most carriers prior to the capture line in both carrier and positive samples 'may' leave a sufficient antigen level in the urines of diseased patients to be detected at capture line of higher antibody concentration. This part of the specification states that it is important to recognize the *lack of any statistically significant figures* showing the level of antigen in the urine of healthy children nasopharyngeally colonized with *Streptococcus pneumoniae* and identifies the necessity for establishing how to screen healthy carriers of pneumococci and children actually having pneumococcal diseases. The specification herein makes the following statements that are indicative of Applicants' future plans and the current belief of what steps might work in a method that is intended to obtain test specificity of 90% or better and increased sensitivity to samples from pneumococcus-infected children with the false positives due to nasopharyngeal pneumococcal colonization eliminated or minimized (see page 16):

> The medically recognized dangers in medicating otherwise healthy carrier children with antibiotics based on false positive test results render it urgent that this work, empirical though it be, continue forward rapidly.
>
> Further test series on urines from other populations of children including nasopharyngeal carriers **are planned** with variations in other test parameters.
>
> Some of them, involving the introduction of at least one scrub line positioned prior to the capture line in the sample flow path of the test devices **are believed to be capable of** being combined with the present concentrations of antibodies on the capture line and in the conjugate that are used in the NOW test.

Clearly, a detection test method that **eliminated 80% of the positive samples**, yielded positive results in as many as **28% to 46% of the urine samples from nasopharyngeal carriers,** and **lacked** statistically significant findings, would result in unnecessary medication of otherwise healthy carrier children who are nasopharyngeal pneumococcal carriers and would result in 'medically recognized dangers' associated such unnecessary medication.

In sum, with Applicants' own disclosure stating how the tested numbers of scrub lines at the tested concentrations of antibodies adversely affected the test results on positive samples from pneumococcus-infected children and decreased the test specificity and sensitivity, and the above-identified Applicants' *future plan*, belief, and speculations, one of skill in the art cannot ascertain that Applicants had possession of a detection method that achieved an art-acceptable test specificity, let alone a test specificity of 90% or better, and an increased sensitivity to samples from pneumococcus-infected children with false positives due to nasopharyngeal pneumococcal colonization minimized, if not eliminated. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089, 118 S. Ct. 1548 (1980), holds that an adequate written description requires 'not a mere wish or plan for obtaining the claimed ……. invention.' *Eli Lilly*, 119 F.3d at 1566. *Vas-Cath Inc. V. Mathukar, 19 USPQ2d 1111* states that Applicant 'must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, is for purposes of the 'written description' inquiry, whatever is now claimed.' See page 1117. What is now claimed was not in Applicants' possession at the time of the invention. The specification does not 'clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.' See page 1116 of *Vas-Cath Inc. V. Mathukar, 19 USPQ2d 1111*. Applicants should also note that *Vas-Cath Inc. V. Mathukar, 19 USPQ2d 1111* makes clear that the written description provision of 35 U.S.C § 112, first paragraph, is severable from its enablement provision. See page 1115. Regardless of the complexity or simplicity of the method, conception cannot be achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that it is a part of the invention. See *Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)* and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016*. The claims are viewed as not meeting the written description provision of 35 U.S.C § 112, first paragraph. The rejection stands.

Remarks

7) Claim 22 stands rejected.

For clarity and proper antecedent basis, it is suggested that Applicants replace the limitation 'a symptomatic .... infection' in the last two lines of the claim with the limitation --the symptomatic .... infection--.

8) **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. The Fax number for submission of amendments, responses and/or papers is (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

10) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

11) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on

Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Robert Mondesi, can be reached on (571) 272-0956.

/S. Devi/
Primary Examiner
AU 1645

August, 2009